FLUORINATED TRICYCLIC NEUROLEPTICS WITH PROLONGED EFFECTS; SOME NEW 8-CHLORO-3-FLUORO--10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b,f*]THIEPINS*

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Six new 8-chloro-3-fluoro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins *II*—*VII* were synthesized, amino alcohol *II* being a highly effective neuroleptic and tranquilizer in acute tests, dioxolane *IV* prolonging these effects upon oral administration. A new synthesis of acid *VIII* was developed, proceeding *via* (2-bromo-4-fluorophenyl)acetic acid (*XI*). A second geometric isomer of the 3--fluoro derivative of chloroprothixene (*XIII*) was prepared which, according to the IR spectrum, is of *cis*-configuration; it is inactive cataleptically and only a weak depressant. Acids *XIVab* were synthesized using selective bromination of phenylacetamide in the *ortho*-position. Starting from acid *XIVa* and *via* the intermediate *XVIIa*, 1-[2-(2-*p*-chlorophenylthiophenyl)-ethyl]-4-methylpiperazine (*XIXa*) was prepared, a new open model of octoclothepin which acted as an anticonvulsant and showed signs of antihistamine effects.

In a previous communication[1] we described the synthesis of the 3-fluoro derivative of octoclothepin (*I*) which displayed a high degree of neuroleptic and depressant activity on oral application in acute tests and clear signs of prolongation of these effects. This was explained by a block of metabolic hydroxylation of the octoclothepin molecule by fluorination[1,2]. The work has now been extended to include several analogues of *I* with modified N-substituents. Firstly, amino alcohol *II* was synthesized, this being a 3-fluoro derivative of the highly active noroxyclothepin[3–5]. It was prepared by a substitution reaction of 8,10-dichloro-3-fluoro-10,11-dihydrodibenzo[*b,f*]-thiepin[1] with 1-(2-hydroxyethyl)piperazine. Its esterification with decanoyl chloride[6] (for method see[4]) yielded the ester *III* which is a 3-fluoro derivative of the depot neuroleptic noroxyclothepin decanoate[4,7,8]. Further prepared were *IV* and *V* with a 1,3-dioxolane or 4-methyl-1,3-dioxolane residue in the side chain; these are 3-fluoro derivatives of previously prepared octoclothepin analogues[9] which displayed, in comparison with octoclothepin, a much lower toxicity on oral administration. The purpose of synthesis of *IV* and *V* was to prepare oral neuroleptics with prolonged effect that would be less toxic than the 3-fluoro derivative of octoclothepin (*I*). For

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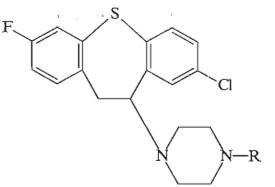
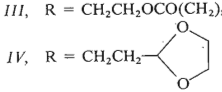
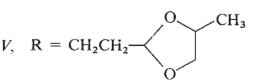
their preparation it was necessary to synthesize the secondary amine *VI* by an established procedure[3] *via* the ethoxycarbonyl derivative *VII*. Products *IV* and *V* were obtained by alkylation of *VI* with 2-(2-chloroethyl)-1,3-dioxolane[10] or with 2-(2-chloroethyl)-4-methyl-1,3-dioxolane[10].



I, R = CH_3
II, R = CH_2CH_2OH
III, R = $CH_2CH_2OCO(CH_2)_8CH_3$



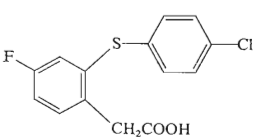
IV, R = CH_2CH_2



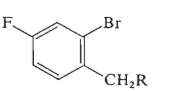
V, R = CH_2CH_2

VI, R = H
VII, R = $COOC_2H_5$

In connection with this work we developed a new synthesis of [2-(4-chlorophenylthio)-4-fluorophenyl]acetic acid (*VIII*) which is a key intermediate of the preparation of the abovementioned 8,10-dichloro-3-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin[1]. Acid *VIII* had been available[1] only from 2-(4-chlorophenylthio)-4-fluorobenzoic



VIII



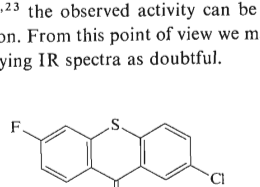
IX, R = Br
X, R = CN

XI, R = COOH
XII, R = $CONH_2$

acid by homologization *via* the alcohol, chloride and nitrile. The new method of preparation of acid *VIII* makes use of the still sufficient reactivity of the bromine atom in (2-bromo-4-fluorophenyl)acetic acid[1] (*XI*) for a reaction with thiophenolates, in our case with potassium 4-chlorothiophenolate. Acid *XI* had not been described and it was obtained as described below from 2-bromo-4-fluorotoluene[11]. Bromination with N-bromosuccinimide yielded 2-bromo-4-fluorobenzyl bromide (*IX*) which reacted with sodium cyanide in dimethylformamide to (2-bromo-4-fluorophenyl)aceto-

nitrile (*X*). Alkaline hydrolysis yielded a satisfactory amount of acid *XI*. An attempt to prepare its amide *XII* by bromination of (4-fluorophenyl)acetamide[12] under conditions when the phenylacetamide is brominated mainly in the *ortho*-position[13,14], was not successful. Bromination does not take place and the original compound is recovered. Amide *XII* was prepared for comparison from acid *XI*. For converting acid *XI* to acid *VIII* we used a reaction of *XI* with 4-chlorothiophenol in the presence of excess potassium carbonate and copper as catalyst in boiling dimethylformamide.

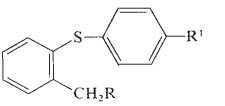
We described before[1] the synthesis of the 6-fluoro derivative of chlorprothixene (*XIII*). The compound is formed by acid-catalyzed dehydration of 2-chloro-6-fluoro--9-(3-dimethylaminopropyl)thioxanthen-9-ol as a mixture of both geometric isomers which were crystallized as hydrochlorides and the major component was thus separated (isomer *A*). On the basis of a band in the IR spectrum at 900 cm^{-1} (for analogy see[15–17]) and of its high neuroleptic activity we ascribed it the structure of the *cis*--isomer (with respect to the position of the chlorine atom and of the side chain). Now the dehydration of the tertiary alcohol was repeated and the mother liquors after the hydrochloride of isomer *A* yielded another homogeneous hydrochloride (isomer *B*) but its IR spectrum also displayed a band at 900 cm^{-1}. For this reason the bases were released from both hydrochlorides and their IR spectra (in carbon disulfide) were compared. The comparison indicates that (because of the intensity of the band at 900 cm^{-1} attributed to the solitary Ar—H in position 1) isomer *B* has a *cis*--configuration while the *A* isomer has a *trans* configuration. This finding is at variance with our earlier observation as well as with the pharmacodynamic activity of isomer *A* and the inactivity of isomer *B* (see below). Since the stereoselectivity of the activity of tricyclic neuroleptics was observed in pairs of geometric isomers[18–21] as well as in the pair of enantiomers[22,23] the observed activity can be used as an argument for attributing the configuration. From this point of view we may regard the conclusions made on the basis of studying IR spectra as doubtful.



XIII

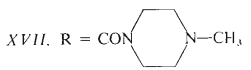
The usefulness of acid *XI* for preparation of acid *VIII* brought us to study (2-bromophenyl)acetic acid from the point of view of synthetic availability and applicability for the preparation of acids *XIVab* which are important intermediates of synthesis of neuroleptic agents octoclothepin[24], methiothepin[25] and oxyprothepin[26]. Preparation of (2-bromophenyl)acetic acid was described in the literature using direct

bromination of phenylacetic acid[27] (it is formed in mixture with the *p*-isomer which is difficult to separate), hydrolysis of (2-bromophenyl)acetonitrile[28] (available in four steps from 2-nitrotoluene), by the Arndt–Eistert reaction from 2-bromobenzoic acid[29] and finally by the action of nitrous acid on (2-bromophenyl)acetamide formed by bromination of phenylacetamide in water[13,14]. (2-Bromophenyl)acetic acid was prepared by hydrolysis of the nitrile[28] and it was condensed with 4-chlorothiophenol by heating with dimethylformamide to 140°C in the presence of anhydrous potassium carbonate and copper; acid *XIVa* was obtained in a 70% yield but the preparation procedure was not more advantageous than the existing methods of preparing acid[24,30] *XIVa*.

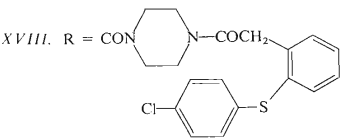


a, $R^1 = Cl$
b, $R^1 = SCH_3$

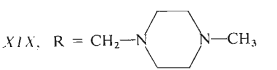
XIV, R = COOH
XV, R = $CONH_2$
XVI, R = $COOC_2H_5$



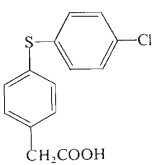
XVII. R = CON N—CH_3



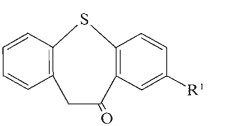
XVIII. R = CON N—$COCH_2$ Cl S



XIX. R = CH_2—N N—CH_3



XX



XXI

The literature[13,14] contains interesting reports on the ready preparation of (2-bromophenyl)acetamide by bromination of phenylacetamide[31] in water. We modified somewhat the bromination conditions which resulted in an increase of the yield to 45%. Gas chromatography showed, however, that the crude product of bromination consists of 75% (2-bromophenyl)acetamide, 10% (4-bromophenyl)acetamide and 15% of the starting phenylacetamide. A single crystallization from 90% ethanol

yields a product consisting of 87% of the 2-bromo isomer, 8% 4-bromo isomer and 5% of the starting phenylacetamide. This was used for further work. Pure (2-bromophenyl)acetamide[32] or the crude product of the above composition reacts with sodium 4-chlorothiophenolate or with 4-chlorothiophenol, or with 4-(methylthio)thiophenol[33] in the presence of potassium carbonate and copper in boiling dimethylformamide or in a melt at 140–160°C, giving rise to amides *XVab*. These may be directly cyclized with the aid of polyphosphoric acid to ketones *XXIab* (this is demonstrated in the experimental section on the example of preparing ketone[24,30] *XXIa*). It was found more suitable, however, to subject amides *XVab* first to alkaline hydrolysis to acids *XIVab*. In one case when crude (2-bromophenyl)acetamide was used, it was possible to isolate from the mother liquor isomeric 4-(4-chlorophenylthio)phenylacetic acid (*XX*). The above procedures represent a fundamental modification of the existing procedure for synthesizing the above neuroleptic preparations.

In this connection we synthesized a new open model of octoclothepin, *i.e.* 1-[2--(2-*p*-chlorophenylthiophenyl)ethyl]-4-methylpiperazine (*XIXa*). The required intermediate, *viz.* methylpiperazide *XVIIa*, was prepared before by a thermal reaction of acid *XIVa* with 1-methylpiperazine[24]. It was found now that a by-product of this reaction was diacylpiperazine *XVIIIa*. As it is formed in a yield of about 10%, its formation cannot be accounted for by the presence of piperazine in the starting 1-methylpiperazine; in the thermal reaction a partial N-demethylation apparently takes place. An attempt was made to prepare methylpiperazide *XVIIa via* the mixed anhydride of acid *XIVa* with carbonic acid monoethyl ester. To this end acid *XIVa* reacted with ethyl chloroformate in chloroform in the presence of triethylamine and the solution formed was treated with 1-methylpiperazine at room temperature. The single product isolated was the ethyl ester *XVIa*. The mixed anhydride apparently was not formed at all while a base-catalyzed re-esterification took place, giving rise to hydrogen chloride (bound by triethylamine) and carbon dioxide as by-products; 1-methylpiperazine did not react with ester *XVIa* under the conditions used. Reduction of methylpiperazide[24] *XVIIa* by lithium aluminium hydride in ether yielded the required amine *XIXa* which was isolated as di(hydrogen maleate).

Compounds *II*, *IV*, *V* and *XIII-B* were evaluated pharmacologically in the form of salts described in the experimental section, with a view to neuroleptic and tranquilizing activity. In all the tests the compounds were administered *per os*. The results of acute tests are shown in Table I. Acute toxicity was determined in female mice in groups of ten animals. Survival was followed up to 7 days. The mean lethal dose LD_{50} is shown in the table. In the rotating-rod test in female mice the incoordinating effect of the compounds was tested; the mean effective doses ED_{50} bringing about ataxia at the time of maximum effect are shown (for *II* 60 min after application, for *IV* after 120 min, for *V* after 45 min, for *XIII-B* after 90 min). The effect on the locomotor activity of male mice was examined by the photo-cell method. For each oral dose five three-animal groups were used. The D_{50} doses decreasing the mean control value of locomotor activity by 50% are shown. The cataleptic effect was tested in female rats. Individual oral doses were administered to groups of 10 animals. The table shows ED_{50} doses bringing about catalepsy of 50% animals.

The antiapomorphine effect was tested in male rats. Groups of 10 animals were given a single dose of compounds corresponding approximately to twice the ED_{50} determined in the catalepsy test. The values shown in the table indicate the percent of inhibition of apomorphine effects from the point of view of chewing and agitation. The control group which was given distilled water *p. o.* represents 100%. All values of the table are results of statistical processing of data obtained for individual animals in the groups. References to pharmacological methods used are given in the earlier paper[1]. The effects mentioned were examined not only immediately but also on the second and third day following application with a view to the expected prolongation of effects. In the antiapomorphine effects, activity was evaluated 4 h after application; 24 h after application none of the compounds tested was inhibitory.

Amino alcohol *II* is highly active in the acute effect both as a central depressant and a neuroleptic; it is superior to octoclothepin as well as to its 3-fluoro derivative. However, it is not interesting from the point of view of prolongation of effects. In the catalepsy test, doses of 0·5–5 mg/kg are active on the 1st day after application in 90% animals while on the second day the effect totally disappears. In the rotating-rod test doses of 0·5–2·5 mg/kg caused ataxia on the first day in 100% animals, on the 2nd day in 20% animals, on the third day it disappeared. In the locomotor activity test doses of 0·1, 0·25 and 0·5 mg/kg caused an inhibition to 61, 55 and 17% of the control, respectively, 1 h after application; after 24 h the respective values were 69, 88 and 70%; after 48 h the effect disappeared.

TABLE I

Pharmacological Effects of New Fluorinated Tricyclic Neuroleptics after Oral Administration to Rats and Mice (doses in mg/kg)

Compound[a]	Code number VÚFB-	Acute toxicity LD_{50}	Rotating rod ED_{50}	Locomotor activity D_{50}	Catalepsy ED_{50}	Antiapomorphine activity (control = 100%)	
						chewing %	agitation %
I[1]	—	28·5	0·8	[b]	3·8	[c]	[c]
II	10·658	[b]	0·8	0·27	1·3	16[d]	19[d]
IV	10·660	110	0·8	0·79	3·2	19[e]	15[e]
V	10·659	135	2·2	0·74	5·0	17[e]	11[e]
XIII-B	10·666	[b]	5·4	3·80	>50[f]	[b]	[b]

[a] The compounds were administered in the form of salts described in the Experimental; the doses given refer to the bases. [b] Was not estimated. [c] The mean effective doses were estimated for this compound.[1] [d] The substance was applied in a dose of 5·0 mg/kg. [e] The substance was applied in a dose of 10·0 mg/kg. [f] In doses of 5, 10, 25 and 50 mg/kg, the substance did not show cataleptic activity.

The dioxolane derivative *IV* displayed the expected rather significant reduction of acute toxicity (in comparison with *I*). In an acute test of the effects it is highly effective as depressant and neuroleptic and it matches compound *I*. It is most interesting from the point of view of prolongation of effects. In the catalepsy test doses of 2·5 to 25 mg/kg are effective in 100% animals on the first day, in 40% animals on the second day and in 10% animals on the third day. In the rotating-rod test doses of 0·5 – 5·0 mg/kg cause ataxia in 100% animals on the first day, in 20% animals on the second day and the effect disappears on the third day. In the locomotor activity test doses of 0·5, 1·5 and 2·5 mg/kg reduce the activity after 1 h to 68, 23 and 10%, respectively. After 24 h, the respective values are 63, 65 and 54%. The highest dose reduces the activity on the third day to 69%.

The dioxolane derivative *V* resembles the previous compound; it is even less toxic but clearly weaker as a depressant and a neuroleptic. In the catalepsy test doses of 1·0 – 10 mg/kg are effective on the first day after application in 70% animals, on the second day in 10% animals and on the third day the effect disappears. In the rotating-rod test doses of 1·0 – 10 mg/kg cause ataxia in 90% animals on the first day, in 30% animals on the second day and the effect disappears on the third day. From the point of view of effect on locomotor activity, doses of 0·5, 1·0 and 2·0 mg/kg reduce the activity after 1 h to 69, 35 and 7%; after 24 h the respective values are 78, 73 and 65%; the highest dose is slightly active even after 48 h (reduction to 95%).

The chlorprothixene derivative *XIII-B* is much less effective than the above compounds in tests for central depressant activity and it is ineffective cataleptically. In doses of 2 – 15 mg/kg it brings about ataxia in 100% animals on the first day and the effect is not prolonged. In the locomotor activity test doses of 2·5, 5 and 10 mg/kg reduce the activity 1 h after application to 62, 45 and 16% of the control; 24 h after application there was an inhibition to 80, 87 and 80%, respectively; after 48 h the effect disappeared. The compound thus shows a certain tranquilizing effect but no neuroleptic effect. This contributes to an earlier observation[23] according to which the depressant effect is not stereospecific while the neuroleptic effect is highly stereospecific.

Ester *III* which, when applied intramuscularly as an oil solution, might prolong the effect on the basis of two mechanisms (as a depot ester[4] and as a compound with blocked degradation through a hydroxylation mechanism[2]) has been tested so far only after oral application as a di-(hydrogen maleate) (VÚFB 12.390). Its oral toxicity LD 50 for mice is 200 mg/kg. It was evaluated by a technique of systematic screening, being applied *in vivo* in a dose of 40 mg/kg. In the rotating-rod test it brings about ataxia in 50% mice at doses of 10 – 40 mg/kg. In the same doses it has hypothermic effect in rats, measured in recto, the temperature drop being by 1°C. In a dose of 10 mg/kg it prolongs thiopental sleep of mice to twice the control values. In Haffner's test doses of 10 to 40 mg/kg cause analgesia in 50% mice. It also has an antihistamine effect in the detoxication test in guinea pigs; doses of 1 – 10 mg/kg protect 50% animals from the lethal effect of intrajugularly applied histamine (5 mg/kg).

The open model of octoclothepin *XIXa* was also tested by the general screening method in the form of di(hydrogen maleate) (VÚFB — 12.389). It was applied *per os*, the LD_{50} being 1·5 g/kg; the basic dose was D = 300 mg/kg. At doses of 100—300 mg/kg it inhibits significantly convulsions caused in mice by pentetrazol. In a dose of 300 mg/kg it acts as an anticonvulsant in the electro-shock test in mice. In hig doses of 100—300 mg/kg it has an antihistamine effect in the histamine detoxication test in guinea pigs. A central depressant effect appears only after application of doses greater than 300 mg/kg.

The compounds prepared were tested from the point of view of antimicrobial effects *in vitro* in the bacteriological department of this institute (Drs J. Turinová and A. Čapek). The results are presented in the usual way in Table II. There is an interesting antituberculosis activity of *II* and *IV* which, however, is displayed in this series rather frequently.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at 0·5 Torr over P_2O_5 at room temperature or at 100°C. IR spectra (in Nujol unless stated otherwise) were recorded in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in CD_3SOCD_3 unless stated otherwise) mostly in a Tesla BS 487C (80 MHz) spectrometer, the mass spectrum in a MS 902 (AEI) spectrometer. Gas-chromatographic analyses were done in a Perkin–Elmer F7 Fractometer. The homogeneity of the compounds was checked by chromatography on a thin layer of silica gel.

2-Bromo-4-fluorobenzyl Bromide (*IX*)

A mixture of 37·4 g 2-bromo-4-fluorotoluene[11] (b.p. 174—175°C), 39 g N-bromosuccinimide and 120 ml CCl_4 was refluxed for 5 h. Two drops of bromine were then added and refluxing continued

TABLE II

Antimicrobial Activity of the Compounds Prepared *in vitro* (the minimum inhibitory concentrations in μg/ml are shown)

Compound[a]	Code number VÚFB-	Microorganism[b]						
		1	2	3	4	5	6	7
II	10·658	25	25	<5	25	50	100	100
III	12·390	>100	>100	100	>100	50	>100	>100
IV	10·660	>100	>100	<5	50	50	100	100
V	10·659	>100	>100	25	100	50	100	100
XIXa	12·389	>100	>100	12·5	50	25	>100	>100

[a] The compounds were used in the form of salts described in the Experimental. [b] 1 *Streptococcus faecalis*, 2 *Staphylococcus pyogenes aureus*, 3 *Mycobacterium tuberculosis* H37Rv, 4 *Saccharomyces pasterianus*, 5 *Trichophyton mentagrophytes*, 6 *Candida albicans*, 7 *Aspergillus niger*. All compounds were inactive (*i.e.* the minimum inhibitory concentration >100 mcg/ml) against *Streptococcus* β-*haemolyticus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus vulgaris*.

for 2·5 h. After standing overnight the precipitated succinimide was filtered and the filtrate evaporated to dryness. The residue (53 g) could be used for further work as such. Distillation yielded 30 g (57%) of the main fraction, boiling at 127—129°C/20 Torr. The distillate crystallized on standing; m.p. 51—52°C. For $C_7H_5Br_2F$ (267·9) calculated: 59·65% Br, 7·09% F; found: 59·20% Br, 7·33% F.

(2-Bromo-4-fluorophenyl)acetonitrile (*X*)

Sodium cyanide (7·5 g) was slowly added to a stirred and cooled solution of 27·4 g *IX* in 40 ml dimethylformamide. After standing overnight it was diluted with water, the precipitated product was filtered, washed with water and dried in air; 21 g (96%), m.p. 62—66°C. The analytical product melted at 70—72°C (cyclohexane). IR spectrum: 828, 882 (2 adjacent and solitary Ar—H), 1489, 1592, 1600 (Ar), 2262 cm^{-1} (R—CN). For C_8H_5BrFN (214·1) calculated: 44·89% C, 2·35% H, 6·54% N; found: 44·72% C, 2·50% H, 6·64% N.

(2-Bromo-4-fluorophenyl)acetic Acid (*XI*)

A solution of 28 g KOH in 60 ml water was added to a solution of 21 g crude *X* in 120 ml ethanol and the mixture was refluxed for 5 h. After standing overnight it was diluted with 500 ml water and the turbid solution was acidified with hydrochloric acid. The crude product was isolated by extraction with chloroform; 19·5 g. Crystallization from a mixture of benzene and light petroleum yielded 12·2 g (53%) product melting at 112—116°C; analytical product, m.p. 116—118°C. IR spectrum: 802, 854, 888 (2 adjacent and solitary Ar—H), 903, 1248 (COOH), 1492, 1595, 1605 (Ar), 1705 (R—COOH), 2560, 2650, 2755 cm^{-1} (COOH). For $C_8H_6BrFO_2$ (233·1) calculated: 41·23% C, 2·59% H; found: 41·36% C, 2·69% H.

(2-Bromo-4-fluorophenyl)acetamide (*XII*)

A mixture of 7·0 g *XI* and 6 ml $SOCl_2$ was refluxed for 1 h, evaporated *in vacuo*, the residue was dissolved in 10 ml acetone and the solution poured into 40 ml concentrated NH_4OH. The precipitated product was filtered (6·7 g) and purified by crystallization from 90% ethanol, m.p. 180 to 181°C. IR spectrum: 800, 872 (2 adjacent and solitary Ar—H), 1492, 1601 (Ar), 1621, 1668 (R—$CONH_2$), 3190, 3390 cm^{-1} (NH_2). For C_8H_7BrFNO (232·1) calculated: 41·40% C, 3·04% H, 34·44% Br, 8·19% F, 6·04% N; found: 41·66% C, 3·06% H, 34·64% Br, 8·02% F, 6·02% N.

[2-(4-Chlorophenylthio)-4-fluorophenyl]acetic Acid (*VIII*)

Potassium carbonate (5·8 g) was slowly added to a stirred mixture of 4·7 g *XI*, 10 ml dimethylformamide, 3·0 g 4-chlorothiophenol and 0·3 g "molecular" copper and the mixture was refluxed for 5 h in a 180°C bath. After cooling, it was diluted with water, filtered and the filtrate was acidified with hydrochloric acid. A total of 5·2 g (87%) crude product, melting at 116—118°C precipitated; after recrystallization the m.p. was 124—125°C (benzene–light petroleum). The compound is identical with the product prepared before[1] by another procedure (m.p. 124—125°C).

8-Chloro-3-fluoro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*II*)

A mixture of 18 g 8,10-dichloro-3-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin[1], 16·4 g 1-(2-hydroxyethyl)piperazine and 30 ml chloroform was refluxed for 5 h, diluted with 200 ml chloroform and

washed with water. Shaking with excess 2% sulfuric acid transferred the product to the aqueous phase which was separated and the base was set free by NH_4OH. Extraction with benzene isolated 18·5 g (78%) of a base; analytical sample, m.p. 116—118°C (cyclohexane), IR spectrum: 815, 838, 880, 890 (2 adjacent and solitary Ar—H), 1 056 (CH_2OH), 1 489, 1 581, 1 590 (Ar), 3 180 cm^{-1} (OH...N). ^{1}H-NMR spectrum (ZKR 60, $CDCl_3$): δ 7·60 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·30 (d, J = 8·0 Hz, 1 H, 6-H), 6·70—7·30 (m, 4 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·58 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00 (s, 1 H, OH), 2·52 (m, 10 H, 5 NCH_2). For $C_{20}H_{22}Cl$ . . FN_2OS (392·9) calculated: 61·13% C, 5·64% H, 7·13% N; found: 61·23% C, 5·70% H, 7·41% N.

Maleate, m.p. 127—129°C (ethanol–ether). For $C_{24}H_{26}ClFN_2O_5S$ (509·0) calculated: 56·63% C, 5·15% H, 6·97% Cl, 5·50% N, 6·30% S; found: 56·52% C, 5·27% H, 7·11% Cl, 5·46% N, 6·45% S.

8-Chloro-10-[4-(2-decanoyloxyethyl)piperazino]-3-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*III*)

Decanoyl chloride[6] (5·1 g) was added dropwise under stirring to a solution of 6·0 g *II* in 9 ml chloroform. After standing overnight, the mixture was diluted with 20 ml chloroform and stirred for 1 h with 50 ml 3% NaOH to remove excess decanoyl chloride. The chloroform solution was separated, dried with K_2CO_3 and filtered with charcoal and evaporated. The remaining oily base was dissolved in 25 ml ethanol and the solution was neutralized while hot with 3·55 g maleic acid; on cooling and standing, 7·4 g (62%) di(hydrogen maleate) precipitated; m.p. 124—126°C. The analytical sample melted at 132—134°C (ethanol). For $C_{38}H_{48}ClFN_2O_{10}S$ (779·3) calculated: 58·56% C, 6·21% H, 4·55% Cl, 2·44% F, 3·60% N, 4·11% S; found: 58·68% C, 6·28% H, 5·07% Cl, 2·40% F, 3·59% N, 4·49% S.

8-Chloro-10-(4-ethoxycarbonylpiperazino)-3-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VII*)

A mixture of 22·4 g 8,10-dichloro-3-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin[1], 24 g 1-ethoxycarbonylpiperazine[34] and 40 ml chloroform was refluxed for 5 h, cooled and diluted with chloroform, washed with water, dried with K_2CO_3 and evaporated. The residue crystallized from 40 ml ethanol to 23·1 g (73%) product, melting at 110—120°C. An analytical sample melted at 120—121°C (ethanol). For $C_{21}H_{22}ClFN_2O_2S$ (420·9) calculated: 59·92% C, 5·27% H, 6·66% N; found: 59·82% C, 5·24% H, 6·63% N.

8-Chloro-3-fluoro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VI*)

A mixture of 23·1 g *VII*, 16 g KOH and 20 ml ethanol was refluxed under stirring in a 120°C bath, diluted with 100 ml water and extracted with benzene. Processing of the extract yielded a crude base which was dissolved in 40 ml ethanol, the solution was neutralized with 7·0 g maleic acid; addition of 40 ml ether precipitated the maleate; 16·8 g (66%), m.p. 163°C under decomposition (ethanol–ether). For $C_{22}H_{22}ClFN_2O_4S$ (465·0) calculated: 56·80% C, 4·77% H, 7·63% Cl, 4·09% F, 6·03% N, 6·91% S; found: 56·93% C, 4·93% H, 7·76% Cl, 4·02% F, 5·96% N, 7·00% S.

Decomposition of the maleate with NH_4OH and extraction with benzene yielded a base, melting at 131—133°C (cyclohexane). ^{1}H-NMR spectrum ($CDCl_3$): δ 7·64 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·29 (d, J = 8·0 Hz, 1 H, 6-H), 6·70—7·30 (m, 4 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·83 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 1·76 (s, disappears after D_2O, 1 H, NH). For $C_{18}H_{18}ClFN_2S$ (348·9) calculated: 61·97% C, 5·20% H, 8·03% N; found: 61·86% C, 5·38% H, 7·94% N.

8-Chloro-10-(4-[2-(1,3-dioxolan-2-yl)ethyl]piperazino)-3-fluoro-10,11-dihydrodibenzo[*b,f*]-thiepin (*IV*)

A mixture of 4·5 g *VI*, 2·7 g 2-(2-chloroethyl)-1,3-dioxolane[10], 1·8 g K_2CO_3 and 5 ml dimethylformamide was refluxed for 5 h under stirring in a 170°C bath; after standing overnight it was diluted with water and the product was extracted with chloroform. The extract was dried with K_2CO_3, filtered with charcoal and evaporated. The residue was dissolved in some benzene and chromatographed on a column of 120 g Al_2O_3 (activity II). Benzene eluted 5·4 g (93%) oily base which was neutralized with maleic acid in ethanol and converted by an addition of ether to di(hydrogen maleate), m.p. 145–147°C (ethanol–ether). ^{1}H-NMR spectrum (ZKR 60): δ 8·90 (bs, 4 H, 4 COOH), 7·00–7·70 (m, 6 H, Ar—H), 6·16 (s, 4 H, 2 CH=CH of maleic acid), 4·90 (t, J = 4·0 Hz, 1 H, O—CH—O), 2·60–4·30 (m, 17 H, 5 NCH_2 + OCH_2CH_2O + $ArCH_2CHAr$), 2·08 (m, 2 H, $CH_2C<^{O}_{O}$). For $C_{31}H_{34}ClFN_2O_{10}S$ (681·1) calculated: 54·66% C, 5·03% H, 5·21% Cl, 2·79% F, 4·11% N, 4·71% S; found: 55·19% C, 5·10% H, 5·17% Cl, 2·87% F, 4·25% N, 4·72% S.

8-Chloro-10-(4-[2-(4-methyl-1,3-dioxolan-2-yl)ethyl]piperazino)-3-fluoro-10,11-dihydro-dibenzo[*b,f*]thiepin (*V*)

Like in the previous case, a reaction of 5·3 g *VI* and 3·5 g 2-(2-chloroethyl)-4-methyl-1,3-dioxolane[10] in 7 ml dimethylformamide in the presence of 3·1 g K_2CO_3 yielded a crude base which was chromatographed on 140 g Al_2O_3 (elution with benzene) and converted to maleate which crystallized from a mixture of 95% ethanol and ether as hemihydrate, m.p. 132–134°C. For $C_{28}H_{32}Cl$ . . FN_2O_6S + 0·5 H_2O (588·1) calculated: 57·18% C, 5·66% H, 6·03% Cl, 4·76% N, 5·45% S; found: 57·42% C, 5·62% H, 5·99% Cl, 4·40% N, 5·38% S.

2-Chloro-9-(3-dimethylaminopropylidene)-6-fluorothioxanthene (*XIII*)

Dehydration of 17·0 g 2-chloro-6-fluoro-9-(3-dimethylaminopropyl)thioxanthen-9-ol[1] was done as described[1]. The crude base obtained (15·4 g) was dissolved in 45 ml ethanol and converted by an ether solution of hydrogen chloride to a mixture of hydrochlorides of both isomers (15·2 g, m.p. 196–217°C). After two crystallizations from ethanol a total of 3·2 g hydrochloride of isomer *A* was obtained, m.p. 229–231°C which is identical with the previously prepared compound[1]. The base (oil) was set free in the usual way and a part of its IR spectrum was examined (in CS_2): 810, infl. 813 (2 adjacent Ar—H), 859 (solitary Ar—H in position 5), 890 cm^{-1} (solitary Ar—H in position 1). In comparison with the spectrum of isomer *B* (see below) the spectrum shows the *A* isomer to be *trans* with respect to the chlorine atom and to the side chain; this is supported by the lower frequency of the solitary Ar—H in position 1 of the skeleton. The conclusion is at variance with the observed pharmacodynamic activity[1].

The mother liquor after the first crystallization of the hydrochloride was evaporated and the residue was crystallized first from a mixture of ethanol and ether, then from alcohol alone. A total of 1·8 g crystals melting at 207–208°C was obtained. These are taken to represent the hydrochloride of isomer *B*. IR spectrum (KBr): 813, 867, 892, 900 (2 adjacent and solitary Ar—H), 1480, 1555, 1598 (Ar), 2495, 2525, 2590 cm^{-1} (NH^+). For $C_{18}H_{18}Cl_2FNS$ (370·3) calculated: 58·38% C, 4·90% H, 3·78% N, 8·66% S: found: 58·47% C, 4·85% H, 3·75% N, 8·46% S. In this case again the oily base was set free; IR spectrum (CS_2): 809, 819 (2 adjacent Ar—H), 859 (solitary Ar—H in position 5), 900 cm^{-1} (solitary Ar—H in position 1). On the basis of the higher frequency of the band of solitary Ar—H in position 1 of the skeleton, isomer *B* is assumed to have a *cis*-configuration. This is again at variance with the observed pharmacodynamic properties.

(2-Bromophenyl)acetamide

Bromine (65 g) was added dropwise under cooling (temperature 10—20°C) to a stirred suspension of 50 g phenylacetamide[31] in 500 ml water. It was then stirred for 5 h at 15—20°C, the excess bromine was removed by adding a solution of $NaHSO_3$, the mixture was cooled to 10°C and, after 30 min of standing, the product was filtered, washed with water and dried in air; 68·5 g. According to gas chromatography it contains 75% of the desired compound, 10% of the 4-isomer and 15% of the starting phenylacetamide. Crystallization from 340 ml 90% ethanol yielded 47 g compound melting at 150—184°C, containing 87% of the desired compound and usable for further work. Further crystallization from ethanol (90%) yielded 35·6 g (45%) pure product melting at 184—186°C (capillary). Ref.[13,14,32] report for the compound m.p. values of 181 to 187°C.

2-(4-Chlorophenylthio)phenylacetamide (*XVa*)

A. Copper (0·4 g) was added at 70°C to a solution of 10·7 g pure (2-bromophenyl)acetamide and 10·0 g sodium 4-chlorothiophenolate in 10 ml dimethylformamide. The mixture was refluxed under stirring for 7 h in a 150°C bath. After partial cooling, it was diluted with 100 ml water, cooled, filtered and washed with water. The solid was extracted with 150 ml boiling ethanol, filtered while hot and the filtrate was evaporated at reduced pressure. The residue crystallized from ethanol to 8·5 g (61%) crude product, melting at 143—145°C. The analytical product melted at 149—151°C (ethanol). IR spectrum: 751, 805 (4 and 2 adjacent Ar—H), 1475, 1609 (Ar), 1665 ($CONH_2$), 3200 and 3385 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 6·80—7·50 (m, 10 H, Ar—H and NH_2), 3·60 (s, 2 H, ArC H_2CO). For $C_{14}H_{12}ClNOS$ (277·8) calculated: 60·53% C, 4·35% H, 12·76% Cl, 5·04% N, 11·55% S; found: 60·82% C, 4·25% H, 12·86% Cl, 5·13% N, 11·64% S.

B. A mixture of 8·6 g pure (2-bromophenyl)acetamide, 6·2 g 4-chlorothiophenol, 8·4 g K_2CO_3, 0·2 g Cu and 6 ml dimethylformamide was stirred for 5 h at 140°C, diluted with 120 ml ethanol, filtered while hot with charcoal and the filtrate was evaporated *in vacuo*. The residue crystallized from 27 ml ethanol to yield 5·0 g (45%) product melting at 143—145°C.

[2-(4-Methylthiophenylthio)phenyl]acetamide (*XVb*)

A mixture of 10·7 g pure (2-bromophenyl)acetamide, 9·0 g 4-(methylthio)thiophenol[33], 6·9 g K_2CO_3, 0·6 g Cu and 10 ml dimethylformamide was refluxed under stirring in a 150°C bath. It was cooled, diluted with 100 ml water, the solid was filtered, washed with water and extracted with 130 ml boiling ethanol. It was filtered while hot and the filtrate was evaporated *in vacuo*. The residue was recrystallized from 30 ml ethanol; 10·8 g (75%), m.p. 130—133°C. The analytical product was obtained by repeated crystallization from ethanol; m.p. 148—149°C. IR spectrum: 747, 812 (4 and 2 adjacent Ar—H), 1575 (Ar), 1650 ($CONH_2$), 3190, 3580 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 6·80—7·40 (m, 10 H, Ar—H and NH_2), 3·80 (s, 2 H, ArCH_2CO), 2·40 (s, 3 H, SCH_3). For $C_{15}H_{15}NOS_2$ (289·4) calculated: 62·25% C, 5·22% H, 4·84% N, 22·16% S; found: 62·61% C, 5·33% H, 4·69% N, 22·00% S.

[2-(4-Chlorophenylthio)phenyl]acetic Acid (*XIVa*)

A. A mixture of 4·3 g (2-bromophenyl)acetic acid[28], 3·2 g 4-chlorothiophenol, 10 ml dimethylformamide, 5·5 g K_2CO_3 and 0·4 g Cu was heated slowly under stirring to 150°C and then stirred for 3·5 h, cooled, diluted with water and filtered. Acidification of the filtrate with hydro-

chloric acid resulted in 3·9 g (70%) crude product melting at 102—108°C; after recrystallization from benzene, it melted at 114—116°C. Ref.[24,30] report for the pure substance a m.p. of 115 to 116°C.

B. A mixture of 21·4 g crude (2-bromophenyl)acetamide (containing 87% pure substance) and 17·3 g 4-chlorothiophenol was heated under stirring to 150°C until a homogeneous melt formed. This was combined in parts with 16·6 g K_2CO_3 and 1 g Cu. The mixture was stirred for 5 h at 150°C, cooled below 100°C, 260 ml ethanol was added and the mixture was refluxed for 30 min. It was filtered while warm and washed with 50 ml ethanol. The filtrate which contains amide *XVa* was combined with 28 g KOH and ethanol was removed by distillation from the mixture over a period of 2 h (a 110—120°C bath). The residue was stirred on a 120°C bath for 3 h, diluted with 400 ml warm water, the solution was filtered while hot with charcoal and the filtrate was acidified with hydrochloric acid. The separated product was isolated by extraction with chloroform and the extract was dried and evaporated. The residue was recrystallized from 28 ml boiling benzene; 16·8 g (69% referred to pure 2-bromophenylacetamide), m.p. 109—115°C. Recrystallization from benzene yielded a pure product melting at 115—116 °C (see *A*).

[4-(4-Chlorophenylthio)phenyl]acetic Acid (*XX*)

Like in the preceding case under *B*, 24 g crude (2-bromophenyl)acetamide (containing 70% pure substance and 18% of the 4-isomer), 17·3 g 4-chlorothiophenol, 17 g K_2CO_3 and 1 g Cu reacted at 140°C. Analogous processing and final crystallization of the residue of the chloroform extract from benzene yielded 11·9 g of a practically pure acid *XIVa* melting at 112—115°C. On dilution of the mother liquor with petroleum ether, 2·0 g crude acid *XX* precipitated; m.p. 131—138°C. It was purified by crystallization from ethanol, m.p. 143—145°C. IR spectrum: 815 (2 adjacent Ar—H), 952, 1250, 1700, 2655, 2730 (COOH), 1478, 1494 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·32 (d, J = 8·0 Hz, 2 H, 2,6-H_2 of the phenyl acetate residue), 7·20 (s, 4 H, Ar—H of 4-chlorophenylene), 7·15 (d, J = 8·0 Hz, 2 H, 3,5-H_2 of phenylacetyl), 3·50 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{11}ClO_2S$ (278·8) calculated: 60·32% C, 3·98% H, 12·72% Cl, 11·50% S; found: 60·26% C, 3·91% H, 12·92% Cl, 11·28% S.

[2-(4-Methylthiophenylthio)phenyl]acetic Acid (*XIVb*)

A mixture of 289 g *XVb*, 280 g KOH, 180 ml water and 280 ml ethanol was refluxed under stirring for 5 h (120°C bath). It was diluted with 3 l hot water, filtered with charcoal, the filtrate was cooled, acidified with hydrochloric acid and extracted with chloroform. Processing of the extract yielded 200 g (69%) crude product which crystallized from a mixture of benzene and light petroleum and melted at 94—108°C. Further crystallization from the same mixture yielded a pure product melting at 117—119°C. Ref.[25] reports the same melting point.

8-Chlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*XXIa*)

A mixture of 3·5 g crude *XVa* (m.p. 143—148°C) with polyphosphoric acid (from 12 g P_2O_5 and 7·5 ml 85% H_3PO_4) was heated for 2 h to 150°C. After dilution with water, it was extracted with chloroform, the extract was washed with 5% NaOH, dried and evaporated; 2·0 g (61%) crude ketone *XXIa*, which crystallizes from ethanol and melts at 119—123°C. On repeating the crystallization, a pure product melting at 125°C was obtained. It is identical with the previously prepared compound[24,30].

Ethyl 2-(4-Chlorophenylthio)phenylacetate (*XVIa*)

Triethylamine (5·1 g) was added to a solution of 13·9 g *XIVa* in 50 ml chloroform. This was followed by a dropwise addition under stirring and cooling of 5·4 g ethyl chloroformate in 10 ml chloroform (over a period of 10 min). The mixture was stirred under cooling for 30 min, a solution of 5·0 g 1-methylpiperazine in 10 ml chloroform was added, the mixture was stirred for 90 min at room temperature, washed with water, with 5% NaOH, dried with K_2CO_3, and chloroform was evaporated. The residue was distilled to yield 11·3 g (74%) ester *XVIa*, boiling at 180°C/0·8 Torr. The distillate crystallized on standing; m.p. 45—47°C (light petroleum). ^{1}H-NMR spectrum ($CDCl_3$): δ c. 7·30 (m, 4 H, Ar—H of phenylacetyl), 7·18 (d, J = 8·0 Hz, 2 H, 3,5-H_2 of 4-chlorophenylene), 7·00 (d, J = 8·0 Hz, 2 H, 2,6-H_2 of chlorophenylene), 4·05 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·78 (s, 2 H, $ArCH_2CO$), 1·18 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{16}H_{15}ClO_2S$ (306·8) calculated: 62·63% C, 4·93% H, 11·56% Cl, 10·45% S; found: 62·81% C, 4·93% H, 11·85% Cl, 10·49% S.

1,4-Bis[2-(4-Chlorophenylthio)phenylacetyl]piperazine (*XVIIIa*)

A mixture of 27·8 g *XIVa* and 12 g 1-methylpiperazine was slowly heated to 200°C and there it was kept for 2 h. The melt was then extracted with 800 ml boiling ethanol and the nondissolved fraction was filtered. On evaporation of the filtrate and processing of the residue according to literature data[24] a methylpiperazide *XVIIa* was obtained which melted at 89—92°C. The ethanol-insoluble fraction (3·2 g, 11%) was purified by crystallization from benzene, m.p. 193—195°C, and identified as *XVIIIa*. IR spectrum: 741, 819 (4 and 2 adjacent Ar—H), 1 477, 1 545, 1 596 (Ar), 1 640 (CON), 3 015, 3 062, 3 075 cm^{-1} (Ar). ^{1}H-NMR spectrum ($CDCl_3$): δ 7·20—7·50 (m, 8 H, Ar—H of *o*-phenylenes), 7·20 (d, J = 8·0 Hz, 4 H, 3,5-H_2 of both 4-chlorophenylenes), 7·00 (d, J = 8·0 Hz, 4 H, 2,6-H_2 of both 4-chlorophenylenes), 3·80 (s, 4 H, 2 $ArCH_2CO$), 3·35 (m, 8 H, 4 NCH_2 of piperazine). Mass spectrum: *m/e* 606·0958 (M^+; low intensity), 463 (60%), 233 (60), 198 (70), 197 (100). For $C_{32}H_{28}Cl_2N_2O_2S_2$ (607·6) calculated: 63·25% C, 4·64% H, 11·67% Cl, 4·61% N, 10·56% S; found: 63·56% C, 4·78% H, 11·49% Cl, 4·28% N, 10·53% S.

1-[2-(2-*p*-Chlorophenylthiophenyl)ethyl]-4-methylpiperazine (*XIXa*)

XVIIa (6·8 g) (ref.[24]) was slowly added to a stirred suspension of 1·1 g $LiAlH_4$ in 70 ml ether and the mixture was refluxed for 4·5 h. After cooling, it was combined with 5 ml water added dropwise and with 1·5 ml 5M-NaOH, the solid was filtered and the filtrate was evaporated. The residue (6·2 g oily base) was dissolved in 210 ml ethanol and the solution was neutralized while hot with a solution of 4·2 g maleic acid in 90 ml water. On cooling and standing, 8·2 g (75%) di(hydrogen maleate) was obtained; m.p. 189—192°C. The analytical sample melted at 193·5—194·5°C (70% ethanol). IR spectrum: 760, 816 (4 and 2 adjacent Ar—H), 1 090, 1 217, 1 354 (COOH), 1 479 (CH_3NH^+), 1 570 (COO^-), 2 380 cm^{-1} (NH^+). For $C_{27}H_{31}ClN_2O_8S$ (579·1) calculated: 56·00% C, 5·40% H, 6·12% Cl, 4·84% N, 5·54% S; found: 56·50% C, 5·63% H, 5·92% Cl, 4·75% N, 5·75% S.

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